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Association of Direct Oral Anticoagulant-Proton Pump Inhibitor Cotherapy with Adverse Outcomes: Protocol for a Population-based Cohort Study

Running title: Drug interaction between DOACs and PPIs

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ABSTRACT

Introduction: Proton pump inhibitors (PPIs) are widely used for secondary prevention of upper gastrointestinal (GI) bleeding. However, there remains controversy about the overall net clinical benefit of PPIs (omeprazole, rabeprazole, pantoprazole, lansoprazole) when co-prescribed with direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, edoxaban). Our objective is to explore the risk of clinically relevant events, including bleeding, thromboembolic events, and death, in patients co-prescribed DOACs and PPIs.

Methods and analysis: The protocol describes a retrospective cohort study of all Ontario residents aged 66 years or older with atrial fibrillation and at least one pharmacy dispensation for a DOAC identified using linked administrative healthcare databases covering 2009 to 2020. Ontario Drug Benefit dispensation records will be used to ascertain PPI exposure during DOAC therapy. The primary outcome is a composite of clinically relevant bleeding, thrombotic events, or all-cause death. Poisson regression with a generalized estimating equation model will be used to calculate the adjusted incidence rate difference, incidence rate ratios 95% confidence interval, adjusting for propensity for PPI use using inverse probability transition weights.

Ethics and dissemination: This research is exempt from REB review under section 45 of Ontario's Personal Health Information Protection Act. We will report our findings in a peer-reviewed biomedical journal and present them at conferences. The study will provide useful evidence to optimize the co-prescription of DOACs and PPIs in practice.

Keywords: Direct oral anticoagulants (DOACs), proton pump inhibitors (PPIs), drug interaction, population-based cohort study.

Word count: 2316

Article Summary

Strengths and limitations of this study

- Few studies explicitly investigate the effects of concomitant PPIs on clinically relevant outcomes (e.g., bleeding, thromboembolic events, and death) in patients receiving direct oral anticoagulants (DOACs).
- In this population-based cohort study of seniors, we examine the risk of thromboembolic adverse events, clinically relevant bleeding, and all-cause death in patients prescribed DOACs when concomitant taking PPIs.
- Time-dependent covariates included in Poisson regression models consider the relation of the survival outcome as a function of the change of the covariate.
- As with any observational study, an important limitation is potential for residual confounding.
- As the study is limited to patients aged ≥66 years, we are unable to generalize the results to younger patients.

INTRODUCTION

Background/rationale

The direct oral anticoagulants (DOACs) refer to the factor Xa inhibitors-rivaroxaban, edoxaban, apixaban, and betrixaban, and the direct thrombin inhibitor-dabigatran.[1] Before introducing DOACs within the last decade, the vitamin-K-antagonist (VKA) warfarin was the only oral anticoagulant used for prevention and treatment of thrombosis.[2] Proton pump inhibitors (PPIs), are H+-K+-blockers, that are used to manage acid-related gastrointestinal (GI) disorders.[3] Currently, there are six PPIs available in Canada: omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and dexlansoprazole. The evidence for PPIs for treating gastroesophageal reflux disease and GI bleeding has been used to indirectly support its concomitant use with DOACs.[4-8] In Canada, with the availability of the DOACs, the proportion of total oral anticoagulant (OAC) prescriptions attributable to warfarin steadily decreased, from 99% in 2010 to around 10% in 2017.[9 10] According to the 2014 guidelines on AF of the Canadian Cardiovascular Society, most patients for whom an OAC is indicated should receive a DOAC rather than warfarin (strong recommendation, high-quality evidence).[11] At the same time, over 33 million prescriptions of PPIs were dispensed in Canada in 2016, and the number is increasing over time.[12] In 2018, direct factor Xa inhibitors and PPIs were among the top 10 drug classes in terms of public drug program spending in seniors: $316.2 million and $180.8 million, respectively.[13]

In a recent systematic review we showed an increased risk of bleeding in patients receiving PPI plus warfarin compared to warfarin alone (OR 1.34, 95% CI, 1.22 -1.47), likely at least partly due to residual confounding.[14] However, controversy remains about the overall net clinical benefit for the PPIs when given with DOACs. Some studies reported no evidence of a protective effect of PPIs against dabigatran-related GI bleeding.[15 16] One large randomized trial showed that pantoprazole treatment in addition to low dose rivaroxaban did not reduce upper GI bleeding.[17] A prospective pilot study demonstrated that the use of dabigatran with PPIs reduced dabigatran plasma levels in patients with AF.[18] Similarly, it was reported that there were no significant changes found in the anticoagulant activity of factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) according to PPI exposure.[19-21] There are several reports of potential pharmacodynamic and pharmacokinetic interactions between PPIs and antithrombotic agents linked to an increase of thromboembolic event.[22-24] However, except for a lower risk of upper GI bleeding, no other clinically meaningful drug-drug interaction (DDIs) with PPIs were reported for DOACs.[25-28]

There is concern that the use of PPIs may reduce the efficacy of DOACs due to alteration of gastric pH as an acidic environment is required for the dissolution of DOACs; the increase in gastric pH induced by PPIs might affect the solubility and absorption of some of the DOACs (i.e., dabigatran and rivaroxaban).[29] In the RE-LY trial, concomitant use of PPIs reduced dabigatran exposure by 15%, but no significant impact on efficacy outcomes was observed.[30] A pilot RCT reported that a 2-week period of PPI withdrawal leads to a significant increase in dabigatran trough and peak plasma levels in patients with AF.[31]

It is important for clinicians to know whether there are clinically relevant effects of the interaction between PPIs and DOACs when they are co-prescribed. Several studies have considered the effects

of cotherapy on GI bleeding.[7 32 33] However, none explicitly investigate the effects of concomitant PPIs on the range of risks and benefits (i.e., clinically relevant gastrointestinal bleeding, thromboembolic events, or death) simultaneously in DOAC-treated patients.

Objectives

The objective of the study is to examine the risk of thromboembolic events, clinically relevant bleeding, and all-cause death in patients concomitantly prescribed DOACs and PPIs.

Our research question is: Among patients receiving DOACs for any indication, does concomitant PPI prescription alter the event rate for the composite outcome (thromboembolic events, clinically relevant bleeding events, and death), compared to not taking PPIs?

METHODS AND ANALYSIS

Study design and data sources

Our study is a population-based cohort study of administrative healthcare data in Ontario, Canada's most populous province. The databases that will be used are listed in Table 1.

We will use Ontario's administrative health databases, which are linked at the person-level using a coded version of the Ontario health insurance number. Prescription drug claims will be identified using the Ontario Drug Benefit Database, which contains comprehensive records of prescriptions dispensed to all Ontarians aged 65 years or older. The Canadian Institute for Health Information (CIHI) Discharge Abstract Database captures diagnostic and procedural information about hospital admissions. The Ontario Health Insurance Plan Registered Persons Database contains demographic and mortality data. OHIP physician claims data will be used to identify physicians' services. Researchers routinely use these databases to study the clinical consequences of drug-drug interactions.[34 35] International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes and International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes will be used to capture the clinical diagnoses associated with healthcare encounters (see **Table 1&Table 2**).

Study Population

Ontario residents aged 66 years or older who are newly dispensed a DOAC (dabigatran, rivaroxaban, edoxaban, apixaban, or betrixaban) from 1 January 2009 to 31 March 2020 will be included. As prescription drug information is available for all adults from their 65th birthday in Ontario, including individuals aged 66 years or older will allow for a 1-year lookback period for existing medications. We will exclude patients with a missing or invalid provincial health insurance number, missing age or sex, and prescription for multiple DOACs at entry. Patients will be censored upon death, hospitalization for bleeding or thrombosis, discontinuation of DOAC, switch to other than the entry DOAC, loss of health insurance, or the end of the study period (31 March 2020), whichever occurs first.

Patient and public involvement

No patient involved.

Main Exposures

We will create a DOAC cohort (the control cohort) and a DOAC-PPI co-therapy cohort (the exposure cohort). Drug exposure with doses will be determined from records of dispensation. Exposure to DOACs and PPIs will be treated as time-varying variables. The drug exposure period will be defined according to the combination of the date the prescription is filled and the prescription duration (days supplied).

We will identify a period of continuous DOAC use for each patient, beginning with the first pharmacy claim for a DOAC following the patient's 66th birthday (index date). Our definition of continuous use is a subsequent prescription within 1.5 times the days supplied of the previous DOAC prescription, using a minimum grace period of 30 days. The risk of DOAC-related bleeding, thromboembolic events, or death will be captured only while patients are taking the index DOAC. Thus, all study analyses will be restricted to periods of anticoagulant treatment during follow-up, defined as the interval from the date the prescription was filled through 1 day after the end of the days of supply, representing approximately two half-lives of the DOACs.

PPI co-therapy will be defined as the period during which gastroprotective effects are most plausible, defined as the interval from filling the prescription (or index date) through the end of the dispensed days of supply. No co-therapy will be defined as person-days with no filled PPI prescription during the observational window.

Main outcomes

The primary outcome will be a composite of clinically relevant bleeding, thrombotic events, or all-cause death. The diagnosis and procedure codes used to define the outcomes can be found in Table 2. Thrombotic events are defined as any thromboembolic event, including myocardial infarction (MI), systemic embolism, ischemic stroke, deep vein thrombosis (DVT), and pulmonary embolism (PE) as captured in hospital discharge abstracts (CIHI-DAD) or emergency department records (NACRS). Clinically relevant bleeding is defined as hospitalization with a most responsible diagnosis, or an emergency department visit with a primary diagnosis of any bleeding. Secondary outcomes include the individual members of the composite primary outcome measure, emergency department visits for the primary outcome, hospitalization for the primary Outcomes will be measured through the records for the hospitalizations and emergency visits registered in the accordingly databases after the index date.

Sample size

We will include up to 26 covariates in the final multivariable Poisson regression models and a minimum of 520 patients (26 covariates × 20) with at least one of the components of the composite outcome (i.e., clinically relevant bleeding, thromboembolic events, or death).[36] To our knowledge, there have been no studies examining rates of the composite outcome of clinically relevant bleeding, thromboembolic events, or death for patients taking DOACs precisely as we have defined them here. However, the sample size is feasible. According to a recently published ICES population-based study, 128,273 patients (average 14,252 annually) were initiated anticoagulation with a DOAC from 2009 to 2017, and 10.5% was reported for the composite outcome (i.e.,

clinically relevant bleedings, thromboembolic events, and death).[37] If the percentage of co-therapy with PPIs is around 35% (264,447 person-years/ 754,389 person-years as reported by Ray et al.),[7] the patients in the co-therapy cohort can reach 5000 annually in ICES databases. During the 10-year observational windows, there should be around 5,250 patients with at least one component event of the composite outcome. Although it will be more than enough to fulfill our target sample size, we will still include any case eligible to perform the final analysis.

Covariates

The potential confounders include patient demographics [age at cohort entry date, sex, urban/rural (RPDB rural variable) at cohort entry, and socioeconomic status (income quintiles: census-based median neighborhood [Dissemination Area] income quintile) at cohort entry date], indications [AF, thromboembolism, valve replacement/repair comorbidities, hip or knee replacement], Charlson Comorbidity Index at entry date, comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, ischemic stroke, transient ischemic attack, dementia, chronic pulmonary disease, anemia, kidney diseases, and hepatic diseases), components of HAS-B_ED score at cohort entry date (hypertension, abnormal kidney or liver function, stroke, bleeding history, and alcohol use)], CHA2 DS2-VASc Score for AF stroke risk at cohort entry date, and the medications relevant to the outcomes (warfarin (yes/no) within 100 days preceding the index date, former PPIs co-therapy consisted of person-days for patients who filled a PPI prescription in the past year, but whose days of supply ended and, thus, should not benefit from co-therapy.

The potential mediators of the proposed covariates during the following-up period include prescription aspirin (time-varying covariable), antiplatelet agents (time-varying covariable), nonsteroidal anti-inflammatory drugs (time-varying covariable), statins (yes/no), antimicrobials (yes/no), and selective serotonin receptor inhibitors (yes/no). Detailed information on covariates is provided in **Table 2**.

Bias

To control for confounding, we will include covariables mentioned above in the model to adjust the results. Furthermore, time-varying exposures will help address potential time-varying confounding.[38] For instance, the doses of our primary exposures (DOACS and PPIs) and prescription of other drugs that may affect outcome risk (e.g., NSAIDs and antiplatelet agents) will be captured in a time-varying fashion on a day-to-day basis, and time-dependent Poisson regression models will be used. In addition, any missing data will be dealt with by multiple imputation should observations be missing in more than 10% of cases.[39]

Data collection

The lookback windows include 1) 365 days for defining new DOAC use, 2) 100 days for other related drugs, 3)180 days to 3 years for disease comorbidities and derived indices, and 4) as per the diagnosis dates in ICES-derive chronic disease cohorts.

Baseline data collection will include age at cohort entry, sex, key medical comorbidities (see Table 2), previous GI bleeding history, indications for DOAC, the name of DOAC and PPIs, the first

prescription date of DOAC (index date), information for covariates, patients who transfer to other DOAC during the observational window, and the type and date of each outcome.

Data analysis

As this is a population-based study, we will include all eligible Ontario residents. We will compare baseline characteristics of exposures and controls using standardized differences. We computed a set of stabilized inverse probability of treatment (IPT) weight to account for differences in the baseline characteristics (Table 2) between the two cohorts.[40] First, the IPT weights were obtained by fitting a logistic regression model with the primary outcome and the DOACs and PPIs co-therapy as independent variables. Next, we applied IPT weights and assessed balance between the two cohorts by calculating weighted standardized differences, which express the difference of means or prevalence between the two cohorts as a proportion of the pooled standard deviation (SD), with standardized differences above 0.10 considered potentially meaningful. The time-dependent Poisson regression model will then be used to estimate the adjusted incidence of the target outcomes according to both exposure cohort and control cohort with all available covariates using the weighted sample[41] and IPT weight adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) will be obtained. The criterion for statistical significance will be set at alpha = 0.05. All statistical analyses will be performed at ICES using SAS version 9.4 (SAS Institute).

Sensitivity analysis will be performed 1) by excluding patients who did not maintain their original DOAC use assignments during their follow-up, and 2) by excluding patients who re-entered the cohort. Subgroup analysis will be performed according to the different DOACs, PPIs, and indications, respectively (if we have enough data).

ETHICS AND DISSEMINATION

This research is exempt from REB review as the data used in the project is authorized under section 45 of Ontario's Personal Health Information Protection Act. Upon completion, the results of this population-based study will be submitted to a peer-reviewed biomedical journal for publication and presented at several conferences.

Collaborators Not applicable.

Author Contributions AH and MW obtained the funding and developed the study idea. MW, AH and MP designed the study. MW obtained data permissions and research ethics approvals. LT, DS, and LM contributed to the study design, methodology and analysis plan. AH and DS provided clinical guidance, AH developed the outcome data sets and MP provided expertise in large administrative health databases housed at ICES in designing the study. MW drafted the initial manuscript, and all authors critiqued the protocol manuscript. All authors approve the attached manuscript for publication and are accountable for all aspects of the work.

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Data statement Not applicable.

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Competing interests None declared.

Patient consent for publication Not required.

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Table 1. Description of the Ontario databases to be used in the study

Name of database	Database description
1. Ontario Drug Benefit (ODB) Plan Database	Records of dispensed outpatient prescriptions paid for by the provincial government. The ODB formulary includes a wide range of routine outpatient medications, including the prescription drugs of interest to this study.
2. Canadian Institute for Health Information–Discharge Abstract Database (CIHI-DAD)	The CIHI-DAD collects diagnostic, and procedural variables for each admission to a hospital in Ontario. Coding of primary and secondary diagnoses and inpatient procedures uses the 10th version of the Canadian Modified International Classification of Diseases (ICD-10 CA) for all diagnoses after 2002.
3. Canadian Institute for Health Information–National Ambulatory Care Reporting System (CIHI-NACRS)	The NACRS is compiled by the Canadian Institute for Health Information (CIHI) and contains administrative, clinical (diagnoses and procedures), demographic, and administrative information for all patient visits made to hospital- and community-based ambulatory care centers (emergency departments, day surgery units, hemodialysis units, and cancer care clinics) in Ontario.
4. Ontario Health Insurance Plan (OHIP) Claims History Database	Claims for physician services paid for by the provincial government. It includes a fee code for each service and a diagnosis code for the condition representing the main reason for each service
5. OHIP Registered Persons Database (RPDB)	The RPDB captures information regarding Ontarians' sex, date of birth, postal code, and vital status.
6. Ontario Mental Health Reporting System (OMHRS)	The OMHRS analyzes and reports on information submitted to CIHI about all individuals receiving hospital-based adult mental health services in Ontario.
7. Same Day Surgery Database (SDS)	The SDS summarizes information about same day surgery encounters. Each record contains the procedures undergone as well as clinical information about the individual. The clinical information follows the ICD coding scheme (ICD-9 before 2002 and ICD-10 from 2002 onwards).
8. Corporate Provider Database (CPDB)	This database contains addresses, registration and program eligibility information (e.g.,

	contracts such as primary care group) about individual health care providers, such as physicians.
9. ICES Physician Database (IPDB)	The IPDB contains information about physicians practicing in Ontario. The IPDB includes demographic information about each physician (i.e., age, sex), practice location, physician specialty, services provided, where each physician was trained and year of graduation.
10. Ontario Census Area Profiles (CENSUS)	Ontario-level demographic and statistical data on individuals and households.
11. Postal Code Conversion File (PCCF)	Links postal codes with Census-based area-level variables such as neighborhood income quintiles and urban/rural residence.
12. Ontario Asthma Database (ASTHMA)	ASTHMA contains all Ontario asthma patients identified since 1991.
13. Ontario Congestive Heart Failure Database (CHF)	The CHF database contains all Ontarians with CHF identified since 1991.
14. Ontario Chronic Obstructive Pulmonary Disease Database (COPD)	COPD contains all Ontario COPD patients identified since 1991.
15. Ontario Hypertension Database (HYPER)	HYPER contains all Ontario hypertension patients identified since 1991.
16. Ontario Dementia Database (DEMENTIA)	The Ontario Dementia Dataset is comprised of all Ontario persons who have been identified with Alzheimer's and related dementias in ICES data holdings between the ages of 40 to 110 years.
17. Ontario Crohn's and Colitis Cohort Database (OCCC)	OCCC includes all Ontario patients who were identified with Crohn's disease or Ulcerative Colitis from the ages of 0-105 years.
18. Ontario Diabetes Database (ODD)	The ODD is a population-based disease registry constructed using a validated algorithm based on hospitalizations and physician visits to identify individuals with physician-diagnosed diabetes mellitus in Ontario.
19. Ontario Rheumatoid Arthritis Database (ORAD)	ORAD contains data on all Ontario rheumatoid arthritis patients identified since 1991.
20. Ontario Cancer Registry (OCR)	Patient demographics, cancer diagnosis details, and death information.

Table 2. Variables and their related data sources with codes (if applicable).

Variables	Data source	Codes or specified
Demographics		
Age & sex	RPDB and CENSUS	Not applicable
Income quintile	Statistics Canada and CENSUS	Not applicable
Rural residence	Census Postal Code Conversion File and CENSUS	Not applicable
Indications		
Atrial fibrillation (AF)	NACRS and DAD	ICD10 I48.0, I48.1, I48.2, I48.3, I48.4, I48.9
Thromboembolism	DAD, NACRS, and OHIP	DAD/NACRS ICD10: I26.0, I26.9, I80.1, I80.2, I80.3, I80.8, I80.9, I82.8, I82.9 OHIP Diagnosis Codes: 415, 451
Valve Replacement/Repair	DAD	DAD CCI : • 1HU90 Mitral valve replacement • 1HU80 Mitral valve repair • 1HV90 Aortic valve replacement • 1HV80 Aortic valve repair • 1HT90 Pulmonary valve replacement • 1HT80 Pulmonary valve repair • 1HS90 Tricuspid valve replacement • 1HS80 Tricuspid valve repair • 1HW Valve annulus surgery
Hip or Knee Replacement	DAD	DAD CCI: • 1VA53 implantation of internal device, hip joint • 1VG53 implantation of internal device; knee joint.
Exposures on a day-to-day basis during the following-up period		
Direct oral anticoagulants (DOACs)	ODB	Rivaroxaban, dabigatran, edoxaban, and apixaban
The proton pump inhibitors (PPIs)	ODB	Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and dexlansoprazole.
Comorbidities		

1. Chronic kidney disease (CKD) in the 3 years prior to cohort entry	CIHI-DAD and OHIP	CIHI-DAD: • I12.0 Hypertensive renal disease with renal failure • I13.1 Hypertensive heart and renal disease with renal failure • N03.X Chronic nephritic syndrome • N05.X Unspecified nephritic syndrome • N18.X Chronic renal failure • N19.X Unspecified renal failure • N25.X Disorders resulting from impaired renal tubular function. OHIP: • 403 Hypertensive renal disease • 585 Chronic renal failure;
2. End stage renal disease (ESRD) in the 180 days prior to cohort entry	DAD/NACRS	DAD/NACRS CCI • 1PZ21HQBR • 1PZ21HPD4 • 1PZ21HQBS. • 1PC85LAXXJ transplant; kidney using living donor (allogenic or syngeneic) kidney • 1PC85LAXXK transplant; kidney using cadaver kidney. OHIP Fee Codes • R849 Dialysis - Hemodialysis - Initial & acute. • G323 Dialysis - Hemodialysis – Acute, repeat (max 3) • G325 Dialysis - Hemodialysis - Medical component (incl in unit fee) • G32 Dialysis - Chronic, contin. hemodialysis or hemofiltration each • G86 Chronic hemodialysis hospital location

		• G862 Hospital self-care Chronic hemodialysis • G863 Chronic hemodialysis IHF location • G86 Chronic Home hemodialysis • G866 Intermittent hemodialysis treatment centre • G330 Peritoneal dialysis - Acute (up to 48 hrs) • G331 Peritoneal dialysis - Repeat acute (up to 48 hrs) max. 3 • G332 Peritoneal dialysis - Chronic (up to 48 hrs) [NOT AFTER JAN 2008] • G861 Chronic peritoneal dialysis hospital location • G864 Chronic Home peritoneal dialysis • G082 Continuous venovenous hemodiafiltration • G083 Continuous venovenous haemodialysis • G085 Continuous venovenous hemofiltration • G090 Venovenous slow continuous ultrafiltration • G091 Continuous arteriovenous haemodialysis • G092 Continuous arteriovenous hemodiafiltration • G093 Hemodiafiltration - Contin. Init & Acute (repeatx3) • G094 Hemodiafiltration - Contin. Chronic • G095 Slow Continuous Ultra Filtration - Initial & Acute (repeat)

		• G096 Slow Continuous Ultra Filtration – Chronic • G294 Arteriovenous slow continuous ultrafiltration init and acute • G295 Continuous arteriovenous hemofiltration initial and acute • G333 Home/self-care dialysis • H540 Renal dialysis (outpatient).
3. Liver disease in the 3 years prior to cohort entry	CIHI-DAD and OHIP	CIHI-DAD: B18.x, K70.x, K71.1, K71.3–K71.5, K71.7, K72.x–K74.x, K76.0, K76.2–K76.9, Z94.4 liver disease. OHIP Diagnosis Code: 571 liver disease.
4. Alcoholism in the 3 years prior to cohort entry	CIHI and OHIP	CIHI: F102, G312, G621, G721, I426, K292, K860, Z8640. OHIP Diagnosis Code: 303
5. Dementia in the 3 years prior to cohort entry	Ontario Dementia Database (DEMENTIA)	Not applicable
6. Diabetes in the 3 years prior to cohort entry in the 3 years prior to cohort entry	Ontario Diabetes Dataset (ODD)	Not applicable
7. Hypertension: Ontario Hypertension Database in the 3 years prior to cohort entry	Ontario Hypertension dataset (HYPER)	Not applicable
8. Congestive heart failure (CHF) in the 3 years prior to cohort entry	Congestive Heart Failure (CHF)	Not applicable
9. Active Cancer	OCR, OHIP	Diagnosis in OCR within 1 year OR any of the following OHIP fee codes within 180 days: chemotherapy: G281, G339, G345, G359, G381, G382, G388; and radiation: X310, X311, X312, X313.
10. $CHADS_2$-VASc Score for Atrial Fibrillation Stroke Risk at cohort entry date	As specified for each code related.	1. Congestive heart failure (CHF database): 1 point 2. Hypertension (HYPER database): 1 point 3. Age 65-74 years: 1 point and age 75 years or older: 2 points

		4. Diabetes Mellitus (Ontario Diabetes Database): 1 point 5. Previous thromboembolism (codes as following in the preceding 3 years): Any or more than 1 of these codes leads to 2 points. Total score can be 0 or 2. 6. Vascular disease (CAD or PVD: CIHI DAD/NACRS: I25x, I70x, I71x, I73x, I74x, K55.1. OHIP: 412, 451in the preceding 3 years): 1 point 7. Female Sex: 1 point
11. HAS-BLED Score at cohort entry date: HAS-B_ED is HAS-BLED without the variable INR (with factors as defined above in the 3-y preceding entry or according to the definition of the ICES-derived cohort)	As specified for each code related.	1. Hypertension (HYPER database): 1 point 2. Abnormal renal function (codes for CKD and ESRD) described above): 1 point 3. Abnormal liver function (codes described above): 1 point 4. Stroke or TIA (CIHI-DAD: I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64, I65, I65.0, I65.1, I65.2, I65.3, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.4, I66.8, I66.9 cerebral infarction (ischemic stroke); G45.0, G45.1, G45.2, G45.3, G45.8, G45.9 transient ischemic attack (TIA)): 1 point 5. Bleeding history (bleeding codes described as following in outcome section): 1 point 6. Elderly: Age over 65: 1 point 7. Alcoholism (codes described above): 1 point
12. Charlson Comorbidity Index (using a 3-year lookback).	DAD	Derived using an ICES-developed macro
Potential drug interactions – dispensed in the past 3 months prior to cohort entry		
1. Warfarin: yes/no	ODB	Not applicable
1. Former PPIs co-therapy: yes/no	ODB	Not applicable

	Potential drug interactions – dispensed during the following up period	
1. Non-steroidal anti-inflammatory drugs*: day-to-day basis	ODB	ibuprofen, naproxen, etodolac, nabumetone, indomethacin, rofecoxib, celecoxib, etoricoxib valdecoxib, and meloxicam
2. Selective serotonin reuptake inhibitors (SSRI): yes/no.	ODB	citalopram, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, mirtazapine, trazodone, amitriptyline, nortriptyline, imipramine, and bupropion
3. Amiodarone	ODB	Not applicable
4. Statins: yes/no.	ODB	Atorvastatin, Fluvastatin, Pravastatin, or Simvastatin
5. Aspirin*: day-to-day basis	ODB	Not applicable
6. Antiplatelets: day-to-day basis	ODB	clopidogrel, ticagrelor, dipyridamole, ticlopidine, or prasugrel
7. Antimicrobials: yes/no.	ODB	Fluconazole, Cephalexin, Cefuroxime, Cotrimoxazole, trimethoprim, Macrolides, Azithromycin, Clarithromycin, Macrolides, Ocular Antibiotics, Amoxicillin, Ampicillin, Penicillins, Gatifloxacin, Ciprofloxacin, Norfloxacin, Quinolones, or Levofloxacin
Outcomes		
Bleeding events	CIHI-DAD and CIHI-NACRS	ICD10 1. Intracranial haemorrhage: I60, I61, I62.0, I62.1, I62.9, S06.400, S06.401, S06.410, S06.411, S06.420, S06.421, S06.430, S06.431, S06.440, S06.441, S06.490, S06.491, S06.500, S06.501, S06.510, S06.511, S06.520, S06.521, S06.530, S06.531, S06.540, S06.541, S06.590, S06.591, S06.600, S06.601, S06.610, S06.611, S06.620, S06.621, S06.630, S06.631, S06.640, S06.641, S06.690, S06.691 2. Eye haemorrhage H35.6, H43.1, H45.0, H11.3, H31.3

		3. Bleeding of respiratory system: R04.0, R04.1, R04.2, R04.8, R04.9, J94.2 4. Upper GI bleeding: I85.0, I98.20, I98.3, K22.10, K22.12, K22.14, K22.16, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.80 5. Lower GI bleeding and general GI bleeding: K62.5, K55.20, K55.21, K63.80, K92.0, K92.1, K92.2 6. Urogenital system bleeding: R31, R310, R311, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N93.0, N93.8, N93.9, N95.0 7. Bleeding of muscular and skeletal systems: M25, M25.00, M25.01, M25.02, M25.03, M25.04, M25.05, M25.06, M25.07, M25.08, M25.09 8. Others: K66.1, N42.1, R58, T79.2, K66.1, D68.3
Thromboembolic event	CIHI-DAD and CIHI-NACRS	ICD10 1. Cerebral infarction (ischemic stroke): I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64, I65, I65.0, I65.1, I65.2, I65.3, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.4, I66.8, I66.9 2. Transient ischemic attack (TIA): G45.0, G45.1, G45.2, G45.3, G45.8, G45.9 3. Retinal vascular occlusions: H34.0, H34.1, H34.2, H34.8, H34.9

		4. Myocardial infarction (MI): I21.1, I21.2, I21.3, I21.4, I21.9, I22.0, I22.1, I22.8, I22.9, I23.0, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8, I24.0, I24.1, I24.8, I24.9 5. Pulmonary embolism (PE): I26.0, I26.9 6. Vascular disorders of intestine: K55.0, K55.1, K55.9 7. Systemic embolism: I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9 8. Atherosclerosis: I70.0, I70.1, I70.2, I7020, I7021, I70.8, I70.9 9. Nontraumatic ischemic infarction of muscle: M62.2 10. Thrombophlebitis: I80.0, I80.1, I80.2, I80.3, I80.8, I80.9, G08 11. Other venous embolism and thrombosis: I82.0, I82.1, I82.2, I82.3, I82.8, I82.9, I81, I67.6 12. Other peripheral vascular diseases: I73.1, I73.8, I73.9
All cause death	RPDB	Not applicable

Abbreviation: the abbreviation for databases refer to Table 1., CCI for Canadian Classification of Interventions codes.

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Association of Direct Oral Anticoagulant-Proton Pump Inhibitor Cotherapy with Adverse Outcomes: Protocol for a Population-based Cohort Study

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Association of Direct Oral Anticoagulant-Proton Pump Inhibitor Cotherapy with Adverse Outcomes: Protocol for a Population-based Cohort Study

Running title: Drug interaction between DOACs and PPIs

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ABSTRACT

Introduction: Proton pump inhibitors (PPIs) are widely used for secondary prevention of upper gastrointestinal (GI) bleeding. However, there remains controversy about the overall net clinical benefit of PPIs (omeprazole, rabeprazole, pantoprazole, lansoprazole) when co-prescribed with direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, edoxaban). Our objective is to explore the risk of clinically relevant events, including bleeding, thromboembolic events, and death, in patients co-prescribed DOACs and PPIs.

Methods and analysis: The protocol describes a retrospective cohort study of all Ontario residents aged 66 years or older with atrial fibrillation and at least one pharmacy dispensation for a DOAC identified using linked administrative healthcare databases covering 2009 to 2020. Ontario Drug Benefit dispensation records will be used to ascertain PPI exposure during DOAC therapy. The primary outcome is a composite of clinically relevant bleeding, thrombotic events, or all-cause death. Poisson regression with a generalized estimating equation model will be used to calculate the adjusted incidence rate difference, incidence rate ratios 95% confidence interval, adjusting for propensity for PPI use using inverse probability of treatment weights.

Ethics and dissemination: This research is exempt from REB review under section 45 of Ontario's Personal Health Information Protection Act. We will report our findings in a peer-reviewed biomedical journal and present them at conferences. The study will provide useful evidence to optimize the co-prescription of DOACs and PPIs in practice.

Keywords: Direct oral anticoagulants (DOACs), proton pump inhibitors (PPIs), drug interaction, population-based cohort study.

Word count: 2501

Strengths and limitations of this study

- This will be a population-based cohort study using Ontario's administrative health databases.
- Exposures and covariates will be time dependent.
- As the study is limited to patients aged >66 years, we cannot generalize the results to younger patients.
- As with any observational study, there is potential for residual confounding.

INTRODUCTION

Background/rationale

The direct oral anticoagulants (DOACs) refer to the factor Xa inhibitors-rivaroxaban, edoxaban, apixaban, and betrixaban, and the direct thrombin inhibitor-dabigatran.[1] Before introducing DOACs within the last decade, the vitamin-K-antagonist (VKA) warfarin was the only oral anticoagulant used for prevention and treatment of thrombosis.[2] Proton pump inhibitors (PPIs), are H+-K+-blockers, that are used to manage acid-related gastrointestinal (GI) disorders.[3] Currently, there are six PPIs available in Canada: omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and dexlansoprazole. The evidence for PPIs for treating gastroesophageal reflux disease and GI bleeding has been used to indirectly support its concomitant use with DOACs.[4-8] In Canada, with the availability of the DOACs, the proportion of total oral anticoagulant (OAC) prescriptions attributable to warfarin steadily decreased, from 99% in 2010 to around 10% in 2017.[9 10] According to the 2014 guidelines on AF of the Canadian Cardiovascular Society, most patients for whom an OAC is indicated should receive a DOAC rather than warfarin (strong recommendation, high-quality evidence).[11] At the same time, over 33 million prescriptions of PPIs were dispensed in Canada in 2016, and the number is increasing over time.[12] In 2018, direct factor Xa inhibitors and PPIs were among the top 10 drug classes in terms of public drug program spending in seniors: $316.2 million and $180.8 million, respectively.[13]

In a recent systematic review we showed an increased risk of bleeding in patients receiving PPI plus warfarin compared to warfarin alone (OR 1.34, 95% CI, 1.22 -1.47), likely at least partly due to residual confounding.[14] However, controversy remains about the overall net clinical benefit for the PPIs when given with DOACs. Some studies reported no evidence of a protective effect of PPIs against dabigatran-related GI bleeding.[15 16] One large randomized trial showed that pantoprazole treatment in addition to low dose rivaroxaban did not reduce upper GI bleeding.[17] A prospective pilot study demonstrated that the use of dabigatran with PPIs reduced dabigatran plasma levels in patients with AF.[18] Similarly, it was reported that there were no significant changes found in the anticoagulant activity of factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) according to PPI exposure.[19-21] There are several reports of potential pharmacodynamic and pharmacokinetic interactions between PPIs and antithrombotic agents linked to an increase of thromboembolic event.[22-24] However, except for a lower risk of upper GI bleeding, no other clinically meaningful drug-drug interaction (DDIs) with PPIs were reported for DOACs.[25-28]

There is concern that the use of PPIs may reduce the efficacy of DOACs due to alteration of gastric pH as an acidic environment is required for the dissolution of DOACs; the increase in gastric pH induced by PPIs might affect the solubility and absorption of some of the DOACs (i.e., dabigatran and rivaroxaban).[29] In the RE-LY trial, concomitant use of PPIs reduced dabigatran exposure by 15%, but no significant impact on efficacy outcomes was observed.[30] A pilot RCT reported that a 2-week period of PPI withdrawal leads to a significant increase in dabigatran trough and peak plasma levels in patients with AF.[31]

It is important for clinicians to know whether there are clinically relevant effects of the interaction between PPIs and DOACs when they are co-prescribed. Several studies have considered the effects

of cotherapy on GI bleeding.[7 32 33] However, none explicitly investigate the effects of concomitant PPIs on the range of risks and benefits (i.e., clinically relevant gastrointestinal bleeding, thromboembolic events, or death) simultaneously in DOAC-treated patients.

Objectives

The objective of the study is to examine the risk of thromboembolic events, clinically relevant bleeding, and all-cause death in patients concomitantly prescribed DOACs and PPIs.

Our research question is: Among patients receiving DOACs for any indication, does concomitant PPI prescription alter the event rate for the composite outcome (thromboembolic events, clinically relevant bleeding events, and death), compared to not taking PPIs?

METHODS AND ANALYSIS

Study design and data sources

Our study is a population-based cohort study of administrative healthcare data in Ontario, Canada's most populous province. The databases that will be used are listed in Table 1.

We will use Ontario's administrative health databases, which are linked at the person-level using a coded version of the Ontario health insurance number. Prescription drug claims will be identified using the Ontario Drug Benefit Database, which contains comprehensive records of prescriptions dispensed to all Ontarians aged 65 years or older. The Canadian Institute for Health Information (CIHI) Discharge Abstract Database captures diagnostic and procedural information about hospital admissions. The Ontario Health Insurance Plan Registered Persons Database contains demographic and mortality data. OHIP physician claims data will be used to identify physicians' services. Researchers routinely use these databases to study the clinical consequences of drug-drug interactions.[34 35] International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes and International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes will be used to capture the clinical diagnoses associated with healthcare encounters (see **Table 1&Table 2**). The planned start and end dates for the study are November 1, 2021, and December 31, 2022, respectively.

Study Population

Ontario residents aged 66 years or older who are newly dispensed a DOAC (dabigatran, rivaroxaban, edoxaban, apixaban, or betrixaban) from 1 January 2009 to 31 March 2020 will be included. As prescription drug information is available for all adults from their 65th birthday in Ontario, including individuals aged 66 years or older will allow for a 1-year lookback period for existing medications. We will exclude patients with a missing or invalid provincial health insurance number, missing age or sex, and prescription for multiple DOACs at entry. Patients will be censored upon death, hospitalization for bleeding or thrombosis, discontinuation of DOAC, switch to other than the entry DOAC, loss of health insurance, or the end of the study period (31 March 2020), whichever occurs first. A study flow diagram is provided in Figure 1.

Patient and public involvement

No patient involved.

Main Exposures

We will create a DOAC cohort (the control cohort) and a DOAC-PPI co-therapy cohort (the exposure cohort). Drug exposure with doses will be determined from records of dispensation. Exposure to DOACs and PPIs will be treated as time-varying variables. The drug exposure period will be defined according to the combination of the date the prescription is filled and the prescription duration (days supplied).

We will identify a period of continuous DOAC use for each patient, beginning with the first pharmacy claim for a DOAC following the patient's 66th birthday (index date). Our definition of continuous use is a subsequent prescription within 1.5 times the days supplied of the previous DOAC prescription, using a minimum grace period of 30 days. The risk of DOAC-related bleeding, thromboembolic events, or death will be captured only while patients are taking the index DOAC. Thus, all study analyses will be restricted to periods of anticoagulant treatment during follow-up, defined as the interval from the date the prescription was filled through 1 day after the end of the days of supply, representing approximately two half-lives of the DOACs.

PPI co-therapy will be defined as the period during which gastroprotective effects are most plausible, defined as the interval from filling the prescription (or index date) through the end of the dispensed days of supply. No co-therapy will be defined as person-days with no filled PPI prescription during the observational window.

Main outcomes

The primary outcome will be a composite of clinically relevant bleeding, thrombotic events, or all-cause death. The diagnosis and procedure codes used to define the outcomes can be found in Table 2. Thrombotic events are defined as any thromboembolic event, including myocardial infarction (MI), systemic embolism, ischemic stroke, deep vein thrombosis (DVT), and pulmonary embolism (PE) as captured in hospital discharge abstracts (CIHI-DAD) or emergency department records (NACRS). Clinically relevant bleeding is defined as hospitalization with a most responsible diagnosis, or an emergency department visit with a primary diagnosis of any bleeding. Secondary outcomes include the individual members of the composite primary outcome measure, emergency department visits for the primary outcome. And hospitalization for the primary outcome. Outcomes will be measured through the records for the hospitalizations and emergency visits registered in the accordingly databases after the index date.

Sample size

We will include up to 26 covariates in the final multivariable Poisson regression models and a minimum of 520 patients (26 covariates × 20) with at least one of the components of the composite outcome (i.e., clinically relevant bleeding, thromboembolic events, or death).[36] To our knowledge, there have been no studies examining rates of the composite outcome of clinically relevant bleeding, thromboembolic events, or death for patients taking DOACs precisely as we have defined them here. However, the sample size is feasible. According to a recently published ICES population-based study, 128,273 patients (average 14,252 annually) were initiated anticoagulation

with a DOAC from 2009 to 2017, and 10.5% was reported for the composite outcome (i.e., clinically relevant bleedings, thromboembolic events, and death).[37] If the percentage of co-therapy with PPIs is around 35% (264,447 person-years/ 754,389 person-years as reported by Ray et al.),[7] the patients in the co-therapy cohort can reach 5000 annually in ICES databases. During the 10-year observational windows, there should be around 5,250 patients with at least one component event of the composite outcome. Although it will be more than enough to fulfill our target sample size, we will still include any case eligible to perform the final analysis.

Covariates

The potential confounders include patient demographics [age at cohort entry date, sex, urban/rural (RPDB rural variable) at cohort entry, and socioeconomic status (income quintiles: census-based median neighborhood [Dissemination Area] income quintile) at cohort entry date], indications [AF, thromboembolism, valve replacement/repair comorbidities, hip or knee replacement], Charlson Comorbidity Index at entry date, comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, ischemic stroke, transient ischemic attack, dementia, chronic pulmonary disease, anemia, kidney diseases, and hepatic diseases), components of HAS-B_ED score at cohort entry date (hypertension, abnormal kidney or liver function, stroke, bleeding history, and alcohol use)], CHA2 DS2-VASc Score for AF stroke risk at cohort entry date, and the medications relevant to the outcomes (warfarin (yes/no) within 100 days preceding the index date, former PPIs co-therapy consisted of person-days for patients who filled a PPI prescription in the past year, but whose days of supply ended and, thus, should not benefit from co-therapy.

The potential mediators of the proposed covariates during the following-up period include prescription aspirin (time-varying covariable), antiplatelet agents (time-varying covariable), nonsteroidal anti-inflammatory drugs (time-varying covariable), statins (yes/no), antimicrobials (yes/no), histamine H2 receptor antagonists (cimetidine, famotidine, nizatidine, sucralfate, and ranitidine) (yes/no), and selective serotonin receptor inhibitors (yes/no). Detailed information on covariates is provided in **Table 2**.

Bias

To control for confounding, we will include covariables mentioned above in the model to adjust the results. Furthermore, time-varying exposures will help address potential time-varying confounding.[38] For instance, the doses of our primary exposures (DOACS and PPIs) and prescription of other drugs that may affect outcome risk (e.g., NSAIDs and antiplatelet agents) will be captured in a time-varying fashion on a day-to-day basis, and time-dependent Poisson regression models will be used. In addition, any missing data will be dealt with by multiple imputation should observations be missing in more than 10% of cases.[39]

Data collection

The lookback windows include 1) 365 days for defining new DOAC use, 2) 100 days for other related drugs, 3)180 days to 3 years for disease comorbidities and derived indices, and 4) as per the diagnosis dates in ICES-derive chronic disease cohorts.

Baseline data collection will include age at cohort entry, sex, key medical comorbidities (see Table 2), previous GI bleeding history, indications for DOAC, the name of DOAC and PPIs, the first prescription date of DOAC (index date), information for covariates, patients who transfer to other DOAC during the observational window, and the type and date of each outcome.

Data analysis

As this is a population-based study, we will include all eligible Ontario residents. We will compare baseline characteristics of exposures and controls using standardized differences. We will compute a set of stabilized inverse probability of treatment (IPT) weight to account for differences in the baseline characteristics (Table 2) between the two cohorts.[40] First, the IPT weights will be obtained by fitting a logistic regression model with the primary outcome and the DOACs and PPIs co-therapy as independent variables. Next, we will apply IPT weights and assessed balance between the two cohorts by calculating weighted standardized differences, which express the difference of means or prevalence between the two cohorts as a proportion of the pooled standard deviation (SD), with standardized differences above 0.10 considered potentially meaningful. The time-dependent Poisson regression model will then be used to estimate the adjusted incidence of the target outcomes according to both exposure cohort and control cohort with all available covariates using the weighted sample[41] and IPT weight adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) will be obtained. The criterion for statistical significance will be set at alpha = 0.05. All statistical analyses will be performed at ICES using SAS version 9.4 (SAS Institute).

Sensitivity analysis will be performed 1) by excluding patients who did not maintain their original DOAC use assignments during their follow-up, and 2) by excluding patients who re-entered the cohort. Subgroup analysis will be performed according to the different DOACs, PPIs, and indications, respectively, sample size permitting.

ETHICS AND DISSEMINATION

This research is exempt from REB review as the data used in the project is authorized under section 45 of Ontario's Personal Health Information Protection Act. The data will be analysed at ICES (www.ices.on.ca) in linked, anonymized form. Upon completion, the results of this population-based study will be submitted to a peer-reviewed biomedical journal for publication and presented at several conferences.

Collaborators Not applicable.

Author Contributions AH and MW obtained the funding and developed the study idea. MW, AH and MP designed the study. MW obtained data permissions and research ethics approvals. LT, DS, and LM contributed to the study design, methodology and analysis plan. AH and DS provided clinical guidance, AH developed the outcome data sets and MP provided expertise in large administrative health databases housed at ICES in designing the study. MW drafted the initial manuscript, and all authors critiqued the protocol manuscript. All authors approve the attached manuscript for publication and are accountable for all aspects of the work.

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Table 1. Description of the Ontario databases to be used in the study

Name of database	Database description
1. Ontario Drug Benefit (ODB) Plan Database	Records of dispensed outpatient prescriptions paid for by the provincial government. The ODB formulary includes a wide range of routine outpatient medications, including the prescription drugs of interest to this study.
2. Canadian Institute for Health Information–Discharge Abstract Database (CIHI-DAD)	The CIHI-DAD collects diagnostic, and procedural variables for each admission to a hospital in Ontario. Coding of primary and secondary diagnoses and inpatient procedures uses the 10th version of the Canadian Modified International Classification of Diseases (ICD-10 CA) for all diagnoses after 2002.
3. Canadian Institute for Health Information–National Ambulatory Care Reporting System (CIHI-NACRS)	The NACRS is compiled by the Canadian Institute for Health Information (CIHI) and contains administrative, clinical (diagnoses and procedures), demographic, and administrative information for all patient visits made to hospital- and community-based ambulatory care centers (emergency departments, day surgery units, hemodialysis units, and cancer care clinics) in Ontario.
4. Ontario Health Insurance Plan (OHIP) Claims History Database	Claims for physician services paid for by the provincial government. It includes a fee code for each service and a diagnosis code for the condition representing the main reason for each service
5. OHIP Registered Persons Database (RPDB)	The RPDB captures information regarding Ontarians' sex, date of birth, postal code, and vital status.
6. Ontario Mental Health Reporting System (OMHRS)	The OMHRS analyzes and reports on information submitted to CIHI about all individuals receiving hospital-based adult mental health services in Ontario.
7. Same Day Surgery Database (SDS)	The SDS summarizes information about same day surgery encounters. Each record contains the procedures undergone as well as clinical information about the individual. The clinical information follows the ICD coding scheme (ICD-9 before 2002 and ICD-10 from 2002 onwards).
8. Corporate Provider Database (CPDB)	This database contains addresses, registration and program eligibility information (e.g.,

	contracts such as primary care group) about individual health care providers, such as physicians.
9. ICES Physician Database (IPDB)	The IPDB contains information about physicians practicing in Ontario. The IPDB includes demographic information about each physician (i.e., age, sex), practice location, physician specialty, services provided, where each physician was trained and year of graduation.
10. Ontario Census Area Profiles (CENSUS)	Ontario-level demographic and statistical data on individuals and households.
11. Postal Code Conversion File (PCCF)	Links postal codes with Census-based area-level variables such as neighborhood income quintiles and urban/rural residence.
12. Ontario Asthma Database (ASTHMA)	ASTHMA contains all Ontario asthma patients identified since 1991.
13. Ontario Congestive Heart Failure Database (CHF)	The CHF database contains all Ontarians with CHF identified since 1991.
14. Ontario Chronic Obstructive Pulmonary Disease Database (COPD)	COPD contains all Ontario COPD patients identified since 1991.
15. Ontario Hypertension Database (HYPER)	HYPER contains all Ontario hypertension patients identified since 1991.
16. Ontario Dementia Database (DEMENTIA)	The Ontario Dementia Dataset is comprised of all Ontario persons who have been identified with Alzheimer's and related dementias in ICES data holdings between the ages of 40 to 110 years.
17. Ontario Crohn's and Colitis Cohort Database (OCCC)	OCCC includes all Ontario patients who were identified with Crohn's disease or Ulcerative Colitis from the ages of 0-105 years.
18. Ontario Diabetes Database (ODD)	The ODD is a population-based disease registry constructed using a validated algorithm based on hospitalizations and physician visits to identify individuals with physician-diagnosed diabetes mellitus in Ontario.
19. Ontario Rheumatoid Arthritis Database (ORAD)	ORAD contains data on all Ontario rheumatoid arthritis patients identified since 1991.
20. Ontario Cancer Registry (OCR)	Patient demographics, cancer diagnosis details, and death information.

Table 2. Variables and their related data sources with codes (if applicable).

Variables	Data source	Codes or specified
Demographics		
Age & sex	RPDB and CENSUS	Not applicable
Income quintile	Statistics Canada and CENSUS	Not applicable
Rural residence	Census Postal Code Conversion File and CENSUS	Not applicable
Indications		
Atrial fibrillation (AF)	NACRS and DAD	ICD10 I48.0, I48.1, I48.2, I48.3, I48.4, I48.9
Thromboembolism	DAD, NACRS, and OHIP	DAD/NACRS ICD10: I26.0, I26.9, I80.1, I80.2, I80.3, I80.8, I80.9, I82.8, I82.9 OHIP Diagnosis Codes: 415, 451
Valve Replacement/Repair	DAD	DAD CCI : • 1HU90 Mitral valve replacement • 1HU80 Mitral valve repair • 1HV90 Aortic valve replacement • 1HV80 Aortic valve repair • 1HT90 Pulmonary valve replacement • 1HT80 Pulmonary valve repair • 1HS90 Tricuspid valve replacement • 1HS80 Tricuspid valve repair • 1HW Valve annulus surgery
Hip or Knee Replacement	DAD	DAD CCI: • 1VA53 implantation of internal device, hip joint • 1VG53 implantation of internal device; knee joint.
Exposures on a day-to-day basis during the following-up period		
Direct oral anticoagulants (DOACs)	ODB	Rivaroxaban, dabigatran, edoxaban, and apixaban
The proton pump inhibitors (PPIs)	ODB	Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and dexlansoprazole.
Comorbidities		

1. Chronic kidney disease (CKD) in the 3 years prior to cohort entry	CIHI-DAD and OHIP	CIHI-DAD: • I12.0 Hypertensive renal disease with renal failure • I13.1 Hypertensive heart and renal disease with renal failure • N03.X Chronic nephritic syndrome • N05.X Unspecified nephritic syndrome • N18.X Chronic renal failure • N19.X Unspecified renal failure • N25.X Disorders resulting from impaired renal tubular function. OHIP: • 403 Hypertensive renal disease • 585 Chronic renal failure;
2. End stage renal disease (ESRD) in the 180 days prior to cohort entry	DAD/NACRS	DAD/NACRS CCI • 1PZ21HQBR • 1PZ21HPD4 • 1PZ21HQBS. • 1PC85LAXXJ transplant; kidney using living donor (allogenic or syngeneic) kidney • 1PC85LAXXK transplant; kidney using cadaver kidney. OHIP Fee Codes • R849 Dialysis - Hemodialysis - Initial & acute. • G323 Dialysis - Hemodialysis – Acute, repeat (max 3) • G325 Dialysis - Hemodialysis - Medical component (incl in unit fee) • G32 Dialysis - Chronic, contin. hemodialysis or hemofiltration each • G86 Chronic hemodialysis hospital location

		• G862 Hospital self-care Chronic hemodialysis • G863 Chronic hemodialysis IHF location • G86 Chronic Home hemodialysis • G866 Intermittent hemodialysis treatment centre • G330 Peritoneal dialysis - Acute (up to 48 hrs) • G331 Peritoneal dialysis - Repeat acute (up to 48 hrs) max. 3 • G332 Peritoneal dialysis - Chronic (up to 48 hrs) [NOT AFTER JAN 2008] • G861 Chronic peritoneal dialysis hospital location • G864 Chronic Home peritoneal dialysis • G082 Continuous venovenous hemodiafiltration • G083 Continuous venovenous haemodialysis • G085 Continuous venovenous hemofiltration • G090 Venovenous slow continuous ultrafiltration • G091 Continuous arteriovenous haemodialysis • G092 Continuous arteriovenous hemodiafiltration • G093 Hemodiafiltration - Contin. Init & Acute (repeatx3) • G094 Hemodiafiltration - Contin. Chronic • G095 Slow Continuous Ultra Filtration - Initial & Acute (repeat)

		• G096 Slow Continuous Ultra Filtration – Chronic • G294 Arteriovenous slow continuous ultrafiltration init and acute • G295 Continuous arteriovenous hemofiltration initial and acute • G333 Home/self-care dialysis • H540 Renal dialysis (outpatient).
3. Liver disease in the 3 years prior to cohort entry	CIHI-DAD and OHIP	CIHI-DAD: B18.x, K70.x, K71.1, K71.3–K71.5, K71.7, K72.x–K74.x, K76.0, K76.2–K76.9, Z94.4 liver disease. OHIP Diagnosis Code: 571 liver disease.
4. Alcoholism in the 3 years prior to cohort entry	CIHI and OHIP	CIHI: F102, G312, G621, G721, I426, K292, K860, Z8640. OHIP Diagnosis Code: 303
5. Dementia in the 3 years prior to cohort entry	Ontario Dementia Database (DEMENTIA)	Not applicable
6. Diabetes in the 3 years prior to cohort entry in the 3 years prior to cohort entry	Ontario Diabetes Dataset (ODD)	Not applicable
7. Hypertension: Ontario Hypertension Database in the 3 years prior to cohort entry	Ontario Hypertension dataset (HYPER)	Not applicable
8. Congestive heart failure (CHF) in the 3 years prior to cohort entry	Congestive Heart Failure (CHF)	Not applicable
9. Active Cancer	OCR, OHIP	Diagnosis in OCR within 1 year OR any of the following OHIP fee codes within 180 days: chemotherapy: G281, G339, G345, G359, G381, G382, G388; and radiation: X310, X311, X312, X313.
10. $CHADS_2$-VASc Score for Atrial Fibrillation Stroke Risk at cohort entry date	As specified for each code related.	1. Congestive heart failure (CHF database): 1 point 2. Hypertension (HYPER database): 1 point 3. Age 65-74 years: 1 point and age 75 years or older: 2 points

		4. Diabetes Mellitus (Ontario Diabetes Database): 1 point 5. Previous thromboembolism (codes as following in the preceding 3 years): Any or more than 1 of these codes leads to 2 points. Total score can be 0 or 2. 6. Vascular disease (CAD or PVD: CIHI DAD/NACRS: I25x, I70x, I71x, I73x, I74x, K55.1. OHIP: 412, 451in the preceding 3 years): 1 point 7. Female Sex: 1 point
11. HAS-BLED Score at cohort entry date: HAS-B_ED is HAS-BLED without the variable INR (with factors as defined above in the 3-y preceding entry or according to the definition of the ICES-derived cohort)	As specified for each code related.	1. Hypertension (HYPER database): 1 point 2. Abnormal renal function (codes for CKD and ESRD) described above): 1 point 3. Abnormal liver function (codes described above): 1 point 4. Stroke or TIA (CIHI-DAD: I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64, I65, I65.0, I65.1, I65.2, I65.3, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.4, I66.8, I66.9 cerebral infarction (ischemic stroke); G45.0, G45.1, G45.2, G45.3, G45.8, G45.9 transient ischemic attack (TIA)): 1 point 5. Bleeding history (bleeding codes described as following in outcome section): 1 point 6. Elderly: Age over 65: 1 point 7. Alcoholism (codes described above): 1 point
12. Charlson Comorbidity Index (using a 3-year lookback).	DAD	Derived using an ICES-developed macro
Potential drug interactions – dispensed in the past 3 months prior to cohort entry		
1. Warfarin: yes/no	ODB	Not applicable
1. Former PPIs co-therapy: yes/no	ODB	Not applicable

	Potential drug interactions – dispensed during the following up period	
1. Non-steroidal anti-inflammatory drugs*: day-to-day basis	ODB	ibuprofen, naproxen, etodolac, nabumetone, indomethacin, rofecoxib, celecoxib, etoricoxib valdecoxib, and meloxicam
2. Selective serotonin reuptake inhibitors (SSRI): yes/no.	ODB	citalopram, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, mirtazapine, trazodone, amitriptyline, nortriptyline, imipramine, and bupropion
3. Amiodarone	ODB	Not applicable
4. Statins: yes/no.	ODB	Atorvastatin, Fluvastatin, Pravastatin, or Simvastatin
5. Aspirin*: day-to-day basis	ODB	Not applicable
6. Antiplatelets: day-to-day basis	ODB	clopidogrel, ticagrelor, dipyridamole, ticlopidine, or prasugrel
7. Antimicrobials: yes/no.	ODB	Fluconazole, Cephalexin, Cefuroxime, Cotrimoxazole, trimethoprim, Macrolides, Azithromycin, Clarithromycin, Macrolides, Ocular Antibiotics, Amoxicillin, Ampicillin, Penicillins, Gatifloxacin, Ciprofloxacin, Norfloxacin, Quinolones, or Levofloxacin
Outcomes		
Bleeding events	CIHI-DAD and CIHI-NACRS	ICD10 1. Intracranial haemorrhage: I60, I61, I62.0, I62.1, I62.9, S06.400, S06.401, S06.410, S06.411, S06.420, S06.421, S06.430, S06.431, S06.440, S06.441, S06.490, S06.491, S06.500, S06.501, S06.510, S06.511, S06.520, S06.521, S06.530, S06.531, S06.540, S06.541, S06.590, S06.591, S06.600, S06.601, S06.610, S06.611, S06.620, S06.621, S06.630, S06.631, S06.640, S06.641, S06.690, S06.691 2. Eye haemorrhage H35.6, H43.1, H45.0, H11.3, H31.3

		3. Bleeding of respiratory system: R04.0, R04.1, R04.2, R04.8, R04.9, J94.2 4. Upper GI bleeding: I85.0, I98.20, I98.3, K22.10, K22.12, K22.14, K22.16, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.80 5. Lower GI bleeding and general GI bleeding: K62.5, K55.20, K55.21, K63.80, K92.0, K92.1, K92.2 6. Urogenital system bleeding: R31, R310, R311, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N93.0, N93.8, N93.9, N95.0 7. Bleeding of muscular and skeletal systems: M25, M25.00, M25.01, M25.02, M25.03, M25.04, M25.05, M25.06, M25.07, M25.08, M25.09 8. Others: K66.1, N42.1, R58, T79.2, K66.1, D68.3
Thromboembolic event	CIHI-DAD and CIHI-NACRS	ICD10 1. Cerebral infarction (ischemic stroke): I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64, I65, I65.0, I65.1, I65.2, I65.3, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.4, I66.8, I66.9 2. Transient ischemic attack (TIA): G45.0, G45.1, G45.2, G45.3, G45.8, G45.9 3. Retinal vascular occlusions: H34.0, H34.1, H34.2, H34.8, H34.9

		4. Myocardial infarction (MI): I21.1, I21.2, I21.3, I21.4, I21.9, I22.0, I22.1, I22.8, I22.9, I23.0, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8, I24.0, I24.1, I24.8, I24.9 5. Pulmonary embolism (PE): I26.0, I26.9 6. Vascular disorders of intestine: K55.0, K55.1, K55.9 7. Systemic embolism: I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9 8. Atherosclerosis: I70.0, I70.1, I70.2, I7020, I7021, I70.8, I70.9 9. Nontraumatic ischemic infarction of muscle: M62.2 10. Thrombophlebitis: I80.0, I80.1, I80.2, I80.3, I80.8, I80.9, G08 11. Other venous embolism and thrombosis: I82.0, I82.1, I82.2, I82.3, I82.8, I82.9, I81, I67.6 12. Other peripheral vascular diseases: I73.1, I73.8, I73.9
All cause death	RPDB	Not applicable

Abbreviation: the abbreviation for databases refer to Table 1., CCI for Canadian Classification of Interventions codes.

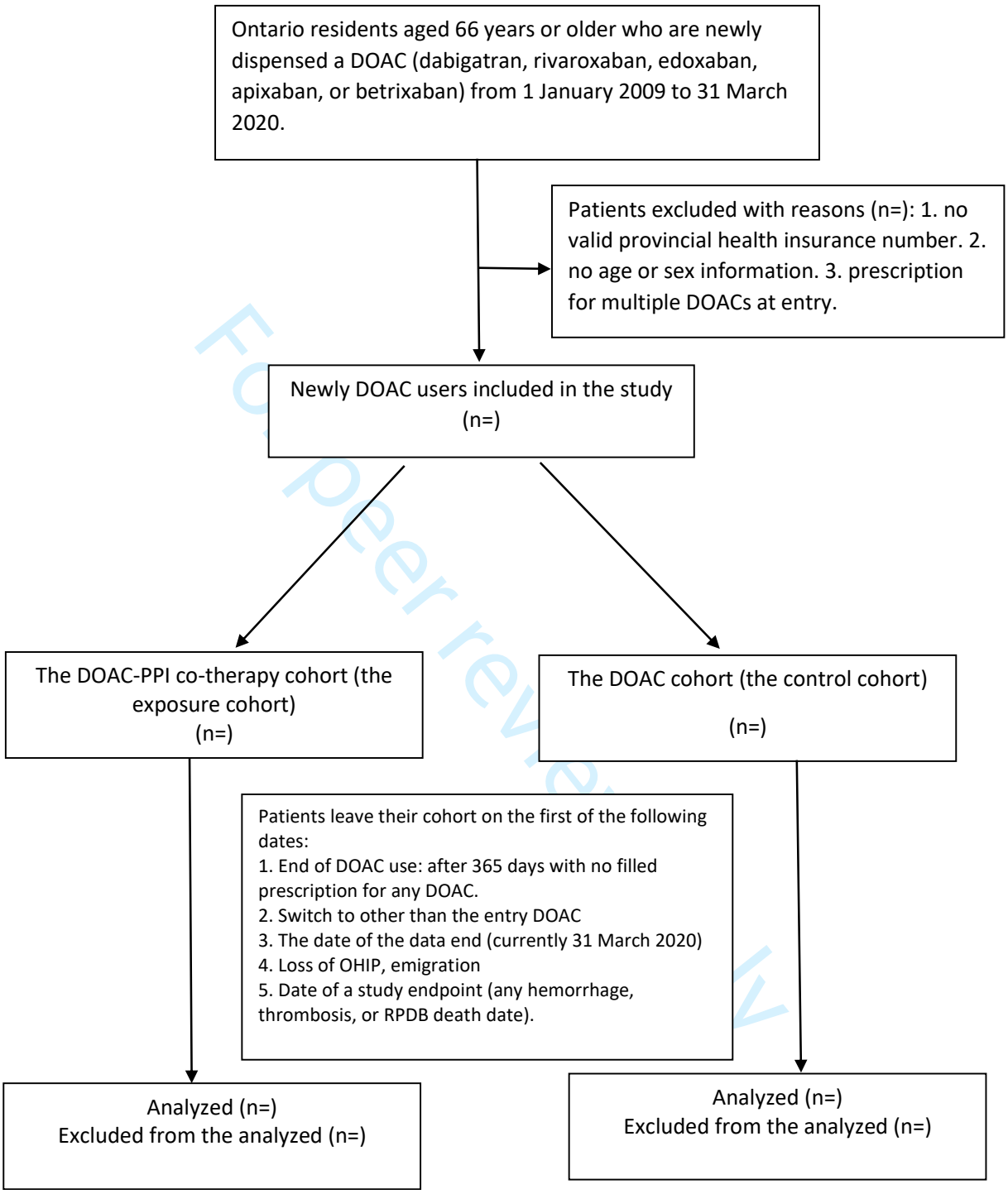

Figure 1. Study flow diagram.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page / lines
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 / 1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	As it is a protocol, n/a
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4 / 32-74
Objectives	3	State specific objectives, including any prespecified hypotheses	4 / 74-79
Methods			
Study design	4	Present key elements of study design early in the paper	4 / 81-83
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4 / 84-95
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4 / 96-105
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5 /108-127 & 6/153-170
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Table 2
Bias	9	Describe any efforts to address potential sources of bias	6 / 171-178
Study size	10	Explain how the study size was arrived at	5-6 / 138-152
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7 / 179-186
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7 / 187-208
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			**As it is a protocol, n/a**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	

		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	n/a
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	n/a
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	n/a
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	n/a
Generalisability	21	Discuss the generalisability (external validity) of the study results	n/a
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8 / 234-238

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Association of Direct Oral Anticoagulant-Proton Pump Inhibitor Cotherapy with Adverse Outcomes: Protocol for a Population-based Cohort Study

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Association of Direct Oral Anticoagulant-Proton Pump Inhibitor Cotherapy with Adverse Outcomes: Protocol for a Population-based Cohort Study

Running title: Drug interaction between DOACs and PPIs

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ABSTRACT

Introduction: Proton pump inhibitors (PPIs) are widely used for secondary prevention of upper gastrointestinal (GI) bleeding. However, there remains controversy about the overall net clinical benefit of PPIs (omeprazole, rabeprazole, pantoprazole, lansoprazole) when co-prescribed with direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, edoxaban). Our objective is to explore the risk of clinically relevant events, including bleeding, thromboembolic events, and death, in patients co-prescribed DOACs and PPIs.

Methods and analysis: The protocol describes a retrospective cohort study of all Ontario residents aged 66 years or older with atrial fibrillation and at least one pharmacy dispensation for a DOAC identified using linked administrative healthcare databases covering 2009 to 2020. Ontario Drug Benefit dispensation records will be used to ascertain PPI exposure during DOAC therapy. The primary outcome is a composite of clinically relevant bleeding, thrombotic events, or all-cause death. A minimum of 520 patients in total with at least one of the components of the composite outcome are needed. Poisson regression with a generalized estimating equation model will be used to calculate the adjusted incidence rate difference, incidence rate ratios 95% confidence interval, adjusting for propensity for PPI use using inverse probability of treatment weights.

Ethics and dissemination: This research is exempt from REB review under section 45 of Ontario's Personal Health Information Protection Act. We will report our findings in a peer-reviewed biomedical journal and present them at conferences. The study will provide useful evidence to optimize the co-prescription of DOACs and PPIs in practice.

Keywords: Direct oral anticoagulants (DOACs), proton pump inhibitors (PPIs), drug interaction, population-based cohort study.

Word count: 2501

Strengths and limitations of this study

- This will be a population-based cohort study using Ontario's administrative health databases.
- Exposures and covariates will be time dependent.
- As the study is limited to patients aged >66 years, we cannot generalize the results to younger patients.
- As with any observational study, there is potential for residual confounding.

INTRODUCTION

Background/rationale

The direct oral anticoagulants (DOACs) refer to the factor Xa inhibitors-rivaroxaban, edoxaban, apixaban, and betrixaban, and the direct thrombin inhibitor-dabigatran.[1] Before introducing DOACs within the last decade, the vitamin-K-antagonist (VKA) warfarin was the only oral anticoagulant used for prevention and treatment of thrombosis.[2] Proton pump inhibitors (PPIs), are H+-K+-blockers, that are used to manage acid-related gastrointestinal (GI) disorders.[3] Currently, there are six PPIs available in Canada: omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and dexlansoprazole. The evidence for PPIs for treating gastroesophageal reflux disease and GI bleeding has been used to indirectly support its concomitant use with DOACs.[4-8] In Canada, with the availability of the DOACs, the proportion of total oral anticoagulant (OAC) prescriptions attributable to warfarin steadily decreased, from 99% in 2010 to around 10% in 2017.[9 10] According to the 2014 guidelines on AF of the Canadian Cardiovascular Society, most patients for whom an OAC is indicated should receive a DOAC rather than warfarin (strong recommendation, high-quality evidence).[11] At the same time, over 33 million prescriptions of PPIs were dispensed in Canada in 2016, and the number is increasing over time.[12] In 2018, direct factor Xa inhibitors and PPIs were among the top 10 drug classes in terms of public drug program spending in seniors: $316.2 million and $180.8 million, respectively.[13]

In a recent systematic review we showed an increased risk of bleeding in patients receiving PPI plus warfarin compared to warfarin alone (OR 1.34, 95% CI, 1.22 -1.47), likely at least partly due to residual confounding.[14] However, controversy remains about the overall net clinical benefit for the PPIs when given with DOACs. Some studies reported no evidence of a protective effect of PPIs against dabigatran-related GI bleeding.[15 16] One large randomized trial showed that pantoprazole treatment in addition to low dose rivaroxaban did not reduce upper GI bleeding.[17] A prospective pilot study demonstrated that the use of dabigatran with PPIs reduced dabigatran plasma levels in patients with AF.[18] Similarly, it was reported that there were no significant changes found in the anticoagulant activity of factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) according to PPI exposure.[19-21] There are several reports of potential pharmacodynamic and pharmacokinetic interactions between PPIs and antithrombotic agents linked to an increase of thromboembolic event.[22-24] However, except for a lower risk of upper GI bleeding, no other clinically meaningful drug-drug interaction (DDIs) with PPIs were reported for DOACs.[25-28]

There is concern that the use of PPIs may reduce the efficacy of DOACs due to alteration of gastric pH as an acidic environment is required for the dissolution of DOACs; the increase in gastric pH induced by PPIs might affect the solubility and absorption of some of the DOACs (i.e., dabigatran and rivaroxaban).[29] In the RE-LY trial, concomitant use of PPIs reduced dabigatran exposure by 15%, but no significant impact on efficacy outcomes was observed.[30] A pilot RCT reported that a 2-week period of PPI withdrawal leads to a significant increase in dabigatran trough and peak plasma levels in patients with AF.[31]

It is important for clinicians to know whether there are clinically relevant effects of the interaction between PPIs and DOACs when they are co-prescribed. Several studies have considered the effects

of cotherapy on GI bleeding.[7 32 33] However, none explicitly investigate the effects of concomitant PPIs on the range of risks and benefits (i.e., clinically relevant gastrointestinal bleeding, thromboembolic events, or death) simultaneously in DOAC-treated patients.

Objectives

The objective of the study is to examine the risk of thromboembolic events, clinically relevant bleeding, and all-cause death in patients concomitantly prescribed DOACs and PPIs.

Our research question is: Among patients receiving DOACs for any indication, does concomitant PPI prescription alter the event rate for the composite outcome (thromboembolic events, clinically relevant bleeding events, and death), compared to not taking PPIs?

METHODS AND ANALYSIS

Study design and data sources

Our study is a population-based cohort study of administrative healthcare data in Ontario, Canada's most populous province. The databases that will be used are listed in Table 1.

We will use Ontario's administrative health databases, which are linked at the person-level using a coded version of the Ontario health insurance number. Prescription drug claims will be identified using the Ontario Drug Benefit Database, which contains comprehensive records of prescriptions dispensed to all Ontarians aged 65 years or older. The Canadian Institute for Health Information (CIHI) Discharge Abstract Database captures diagnostic and procedural information about hospital admissions. The Ontario Health Insurance Plan Registered Persons Database contains demographic and mortality data. OHIP physician claims data will be used to identify physicians' services. Researchers routinely use these databases to study the clinical consequences of drug-drug interactions.[34 35] International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes and International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes will be used to capture the clinical diagnoses associated with healthcare encounters (see **Table 1&Appendix**). The planned start and end dates for the study are November 1, 2021, and December 31, 2022, respectively.

Study Population

Ontario residents aged 66 years or older who are newly dispensed a DOAC (dabigatran, rivaroxaban, edoxaban, apixaban, or betrixaban) from 1 January 2009 to 31 March 2020 will be included. As prescription drug information is available for all adults from their 65th birthday in Ontario, including individuals aged 66 years or older will allow for a 1-year lookback period for existing medications. We will exclude patients with a missing or invalid provincial health insurance number, missing age or sex, and prescription for multiple DOACs at entry. Patients will be censored upon death, hospitalization for bleeding or thrombosis, discontinuation of DOAC, switch to other than the entry DOAC, loss of health insurance, or the end of the study period (31 March 2020), whichever occurs first. A study flow diagram is provided in Figure 1.

Patient and public involvement

No patient involved.

Main Exposures

We will create a DOAC cohort (the control cohort) and a DOAC-PPI co-therapy cohort (the exposure cohort). Drug exposure with doses will be determined from records of dispensation. Exposure to DOACs and PPIs will be treated as time-varying variables. The drug exposure period will be defined according to the combination of the date the prescription is filled and the prescription duration (days supplied).

We will identify a period of continuous DOAC use for each patient, beginning with the first pharmacy claim for a DOAC following the patient's 66th birthday (index date). Our definition of continuous use is a subsequent prescription within 1.5 times the days supplied of the previous DOAC prescription, using a minimum grace period of 30 days. The risk of DOAC-related bleeding, thromboembolic events, or death will be captured only while patients are taking the index DOAC. Thus, all study analyses will be restricted to periods of anticoagulant treatment during follow-up, defined as the interval from the date the prescription was filled through 1 day after the end of the days of supply, representing approximately two half-lives of the DOACs.

PPI co-therapy will be defined as the period during which gastroprotective effects are most plausible, defined as the interval from filling the prescription (or index date) through the end of the dispensed days of supply. No co-therapy will be defined as person-days with no filled PPI prescription during the observational window.

Main outcomes

The primary outcome will be a composite of clinically relevant bleeding, thrombotic events, or all-cause death. The diagnosis and procedure codes used to define the outcomes can be found in Appendix. Thrombotic events are defined as any thromboembolic event, including myocardial infarction (MI), systemic embolism, ischemic stroke, deep vein thrombosis (DVT), and pulmonary embolism (PE) as captured in hospital discharge abstracts (CIHI-DAD) or emergency department records (NACRS). Clinically relevant bleeding is defined as hospitalization with a most responsible diagnosis, or an emergency department visit with a primary diagnosis of any bleeding. Secondary outcomes include the individual members of the composite primary outcome measure, emergency department visits for the primary outcome. And hospitalization for the primary outcome. Outcomes will be measured through the records for the hospitalizations and emergency visits registered in the accordingly databases after the index date.

Sample size

We will include up to 26 covariates in the final multivariable Poisson regression models and a minimum of 520 patients (26 covariates × 20) with at least one of the components of the composite outcome (i.e., clinically relevant bleeding, thromboembolic events, or death).[36] To our knowledge, there have been no studies examining rates of the composite outcome of clinically relevant bleeding, thromboembolic events, or death for patients taking DOACs precisely as we have defined them here. However, the sample size is feasible. According to a recently published ICES population-based study, 128,273 patients (average 14,252 annually) were initiated anticoagulation

with a DOAC from 2009 to 2017, and 10.5% was reported for the composite outcome (i.e., clinically relevant bleedings, thromboembolic events, and death).[37] If the percentage of co-therapy with PPIs is around 35% (264,447 person-years/ 754,389 person-years as reported by Ray et al.),[7] the patients in the co-therapy cohort can reach 5000 annually in ICES databases. During the 10-year observational windows, there should be around 5,250 patients with at least one component event of the composite outcome. Although it will be more than enough to fulfill our target sample size, we will still include any case eligible to perform the final analysis.

Covariates

The potential confounders include patient demographics [age at cohort entry date, sex, urban/rural (RPDB rural variable) at cohort entry, and socioeconomic status (income quintiles: census-based median neighborhood [Dissemination Area] income quintile) at cohort entry date], indications [AF, thromboembolism, valve replacement/repair comorbidities, hip or knee replacement], Charlson Comorbidity Index at entry date, comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, ischemic stroke, transient ischemic attack, dementia, chronic pulmonary disease, anemia, kidney diseases, and hepatic diseases), components of HAS-B_ED score at cohort entry date (hypertension, abnormal kidney or liver function, stroke, bleeding history, and alcohol use)], CHA2 DS2-VASc Score for AF stroke risk at cohort entry date, and the medications relevant to the outcomes (warfarin (yes/no) within 100 days preceding the index date, former PPIs co-therapy consisted of person-days for patients who filled a PPI prescription in the past year, but whose days of supply ended and, thus, should not benefit from co-therapy.

The potential mediators of the proposed covariates during the following-up period include prescription aspirin (time-varying covariable), antiplatelet agents (time-varying covariable), nonsteroidal anti-inflammatory drugs (time-varying covariable), statins (yes/no), antimicrobials (yes/no), histamine H2 receptor antagonists (cimetidine, famotidine, nizatidine, sucralfate, and ranitidine) (yes/no), and selective serotonin receptor inhibitors (yes/no). Detailed information on covariates is provided in **Appendix**.

Bias

To control for confounding, we will include covariables mentioned above in the model to adjust the results. Furthermore, time-varying exposures will help address potential time-varying confounding.[38] For instance, the doses of our primary exposures (DOACS and PPIs) and prescription of other drugs that may affect outcome risk (e.g., NSAIDs and antiplatelet agents) will be captured in a time-varying fashion on a day-to-day basis, and time-dependent Poisson regression models will be used. However, one of the key limitations of any observational study is the risk of residual confounding, even after all potential adjustments are made. In addition, any missing data will be dealt with by multiple imputation should observations be missing in more than 10% of cases.[39]

Data collection

The lookback windows include 1) 365 days for defining new DOAC use, 2) 100 days for other related drugs, 3)180 days to 3 years for disease comorbidities and derived indices, and 4) as per the diagnosis dates in ICES-derive chronic disease cohorts.

Baseline data collection will include age at cohort entry, sex, key medical comorbidities (see Appendix), previous GI bleeding history, indications for DOAC, the name of DOAC and PPIs, the first prescription date of DOAC (index date), information for covariates, patients who transfer to other DOAC during the observational window, and the type and date of each outcome.

Data analysis

As this is a population-based study, we will include all eligible Ontario residents. We will compare baseline characteristics of exposures and controls using standardized differences. We will compute a set of stabilized inverse probability of treatment (IPT) weight to account for differences in the baseline characteristics (Appendix) between the two cohorts.[40] First, the IPT weights will be obtained by fitting a logistic regression model with the primary outcome and the DOACs and PPIs co-therapy as independent variables. Next, we will apply IPT weights and assessed balance between the two cohorts by calculating weighted standardized differences, which express the difference of means or prevalence between the two cohorts as a proportion of the pooled standard deviation (SD), with standardized differences above 0.10 considered potentially meaningful. The time-dependent Poisson regression model will then be used to estimate the adjusted incidence of the target outcomes according to both exposure cohort and control cohort with all available covariates using the weighted sample[41] and IPT weight adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) will be obtained. The criterion for statistical significance will be set at alpha = 0.05. All statistical analyses will be performed at ICES using SAS version 9.4 (SAS Institute).

Sensitivity analysis will be performed 1) by excluding patients who did not maintain their original DOAC use assignments during their follow-up, and 2) by excluding patients who re-entered the cohort. Subgroup analysis will be performed according to the different DOACs, PPIs, and indications, respectively, sample size permitting.

ETHICS AND DISSEMINATION

This research is exempt from REB review as the data used in the project is authorized under section 45 of Ontario's Personal Health Information Protection Act. The data will be analysed at ICES (www.ices.on.ca) in linked, anonymized form. Upon completion, the results of this population-based study will be submitted to a peer-reviewed biomedical journal for publication and presented at several conferences.

Collaborators Not applicable.

Author Contributions AH and MW obtained the funding and developed the study idea. MW, AH and MP designed the study. MW obtained data permissions and research ethics approvals. LT (Lehana Thabane), DS, Laura Targownik (LT) and LM contributed to the study design, methodology and analysis plan. AH and DS provided clinical guidance, AH developed the

outcome data sets and MP provided expertise in large administrative health databases housed at ICES in designing the study. MW drafted the initial manuscript, and all authors critiqued the protocol manuscript. All authors approve the attached manuscript for publication and are accountable for all aspects of the work.

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Data statement Not applicable.

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Figure legend

Figure 1. Study flow diagram.

Table 1. Description of the Ontario databases to be used in the study

Name of database	Database description
1. Ontario Drug Benefit (ODB) Plan Database	Records of dispensed outpatient prescriptions paid for by the provincial government. The ODB formulary includes a wide range of routine outpatient medications, including the prescription drugs of interest to this study.
2. Canadian Institute for Health Information–Discharge Abstract Database (CIHI-DAD)	The CIHI-DAD collects diagnostic, and procedural variables for each admission to a hospital in Ontario. Coding of primary and secondary diagnoses and inpatient procedures uses the 10th version of the Canadian Modified International Classification of Diseases (ICD-10 CA) for all diagnoses after 2002.
3. Canadian Institute for Health Information–National Ambulatory Care Reporting System (CIHI-NACRS)	The NACRS is compiled by the Canadian Institute for Health Information (CIHI) and contains administrative, clinical (diagnoses and procedures), demographic, and administrative information for all patient visits made to hospital- and community-based ambulatory care centers (emergency departments, day surgery units, hemodialysis units, and cancer care clinics) in Ontario.
4. Ontario Health Insurance Plan (OHIP) Claims History Database	Claims for physician services paid for by the provincial government. It includes a fee code for each service and a diagnosis code for the condition representing the main reason for each service
5. OHIP Registered Persons Database (RPDB)	The RPDB captures information regarding Ontarians' sex, date of birth, postal code, and vital status.
6. Ontario Mental Health Reporting System (OMHRS)	The OMHRS analyzes and reports on information submitted to CIHI about all individuals receiving hospital-based adult mental health services in Ontario.
7. Same Day Surgery Database (SDS)	The SDS summarizes information about same day surgery encounters. Each record contains the procedures undergone as well as clinical information about the individual. The clinical information follows the ICD coding scheme (ICD-9 before 2002 and ICD-10 from 2002 onwards).
8. Corporate Provider Database (CPDB)	This database contains addresses, registration and program eligibility information (e.g., contracts such as primary care group) about individual health care providers, such as physicians.
9. ICES Physician Database (IPDB)	The IPDB contains information about physicians practicing in Ontario. The IPDB includes demographic information about each physician

	(i.e., age, sex), practice location, physician specialty, services provided, where each physician was trained and year of graduation.
10. Ontario Census Area Profiles (CENSUS)	Ontario-level demographic and statistical data on individuals and households.
11. Postal Code Conversion File (PCCF)	Links postal codes with Census-based area-level variables such as neighborhood income quintiles and urban/rural residence.
12. Ontario Asthma Database (ASTHMA)	ASTHMA contains all Ontario asthma patients identified since 1991.
13. Ontario Congestive Heart Failure Database (CHF)	The CHF database contains all Ontarians with CHF identified since 1991.
14. Ontario Chronic Obstructive Pulmonary Disease Database (COPD)	COPD contains all Ontario COPD patients identified since 1991.
15. Ontario Hypertension Database (HYPER)	HYPER contains all Ontario hypertension patients identified since 1991.
16. Ontario Dementia Database (DEMENTIA)	The Ontario Dementia Dataset is comprised of all Ontario persons who have been identified with Alzheimer's and related dementias in ICES data holdings between the ages of 40 to 110 years.
17. Ontario Crohn's and Colitis Cohort Database (OCCC)	OCCC includes all Ontario patients who were identified with Crohn's disease or Ulcerative Colitis from the ages of 0-105 years.
18. Ontario Diabetes Database (ODD)	The ODD is a population-based disease registry constructed using a validated algorithm based on hospitalizations and physician visits to identify individuals with physician-diagnosed diabetes mellitus in Ontario.
19. Ontario Rheumatoid Arthritis Database (ORAD)	ORAD contains data on all Ontario rheumatoid arthritis patients identified since 1991.
20. Ontario Cancer Registry (OCR)	Patient demographics, cancer diagnosis details, and death information.

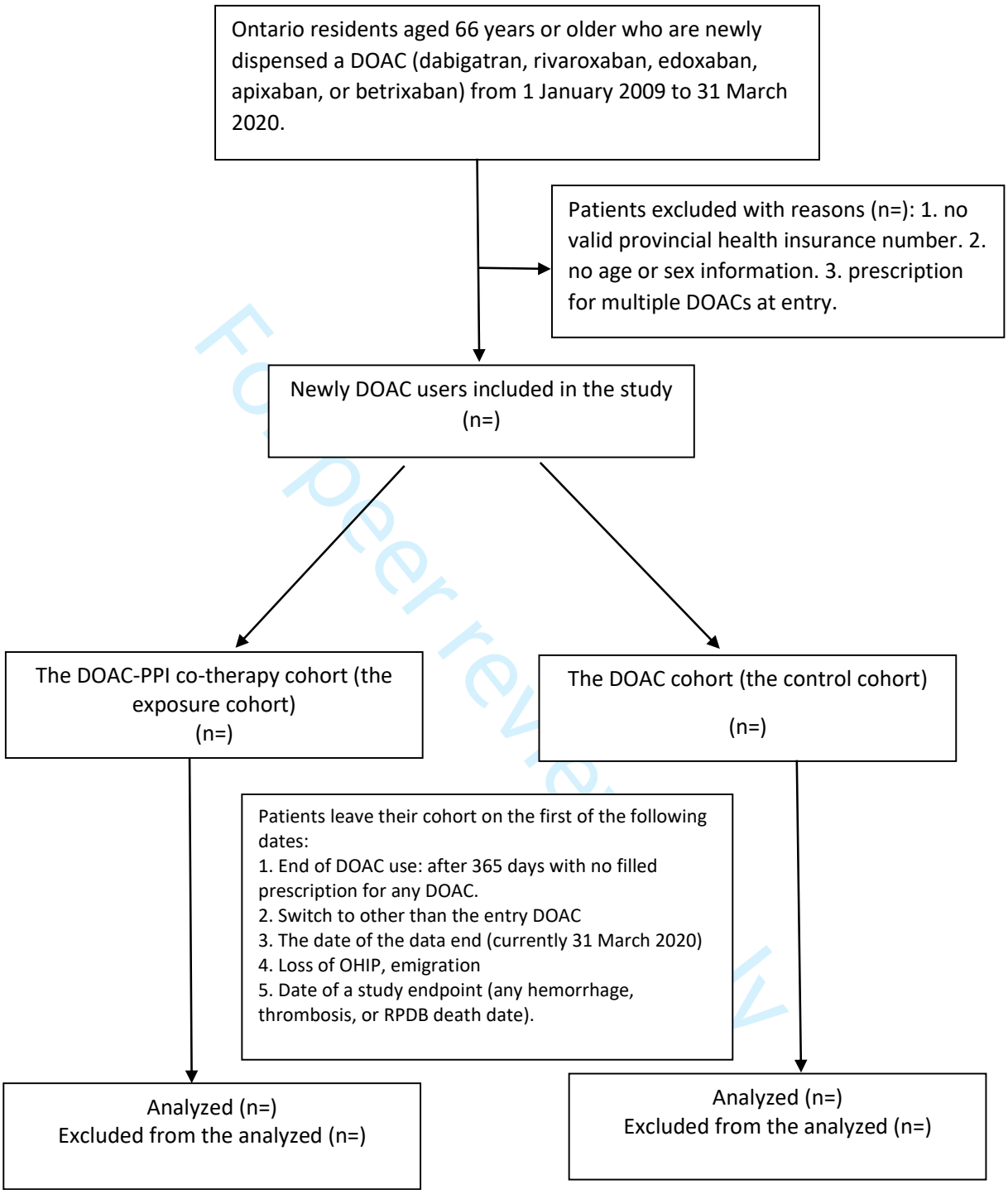

Figure 1. Study flow diagram.

Appendix. Variables and their related data sources with codes (if applicable).

Variables	Data source	Codes or specified
Demographics		
Age & sex	RPDB and CENSUS	Not applicable
Income quintile	Statistics Canada and CENSUS	Not applicable
Rural residence	Census Postal Code Conversion File and CENSUS	Not applicable
Indications		
Atrial fibrillation (AF)	NACRS and DAD	ICD10 I48.0, I48.1, I48.2, I48.3, I48.4, I48.9
Thromboembolism	DAD, NACRS, and OHIP	DAD/NACRS ICD10: I26.0, I26.9, I80.1, I80.2, I80.3, I80.8, I80.9, I82.8, I82.9 OHIP Diagnosis Codes: 415, 451
Valve Replacement/Repair	DAD	DAD CCI : • 1HU90 Mitral valve replacement • 1HU80 Mitral valve repair • 1HV90 Aortic valve replacement • 1HV80 Aortic valve repair • 1HT90 Pulmonary valve replacement • 1HT80 Pulmonary valve repair • 1HS90 Tricuspid valve replacement • 1HS80 Tricuspid valve repair • 1HW Valve annulus surgery
Hip or Knee Replacement	DAD	DAD CCI: • 1VA53 implantation of internal device, hip joint • 1VG53 implantation of internal device; knee joint.
Exposures on a day-to-day basis during the following-up period		
Direct oral anticoagulants (DOACs)	ODB	Rivaroxaban, dabigatran, edoxaban, and apixaban
The proton pump inhibitors (PPIs)	ODB	Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and dexlansoprazole.
Comorbidities		

1. Chronic kidney disease (CKD) in the 3 years prior to cohort entry	CIHI-DAD and OHIP	CIHI-DAD: • I12.0 Hypertensive renal disease with renal failure • I13.1 Hypertensive heart and renal disease with renal failure • N03.X Chronic nephritic syndrome • N05.X Unspecified nephritic syndrome • N18.X Chronic renal failure • N19.X Unspecified renal failure • N25.X Disorders resulting from impaired renal tubular function. OHIP: • 403 Hypertensive renal disease • 585 Chronic renal failure;
2. End stage renal disease (ESRD) in the 180 days prior to cohort entry	DAD/NACRS	DAD/NACRS CCI • 1PZ21HQBR • 1PZ21HPD4 • 1PZ21HQBS. • 1PC85LAXXJ transplant; kidney using living donor (allogenic or syngeneic) kidney • 1PC85LAXXK transplant; kidney using cadaver kidney. OHIP Fee Codes • R849 Dialysis - Hemodialysis - Initial & acute. • G323 Dialysis - Hemodialysis – Acute, repeat (max 3) • G325 Dialysis - Hemodialysis - Medical component (incl in unit fee) • G32 Dialysis - Chronic, contin. hemodialysis or hemofiltration each • G86 Chronic hemodialysis hospital location

		• G862 Hospital self-care Chronic hemodialysis • G863 Chronic hemodialysis IHF location • G86 Chronic Home hemodialysis • G866 Intermittent hemodialysis treatment centre • G330 Peritoneal dialysis - Acute (up to 48 hrs) • G331 Peritoneal dialysis - Repeat acute (up to 48 hrs) max. 3 • G332 Peritoneal dialysis - Chronic (up to 48 hrs) [NOT AFTER JAN 2008] • G861 Chronic peritoneal dialysis hospital location • G864 Chronic Home peritoneal dialysis • G082 Continuous venovenous hemodiafiltration • G083 Continuous venovenous haemodialysis • G085 Continuous venovenous hemofiltration • G090 Venovenous slow continuous ultrafiltration • G091 Continuous arteriovenous haemodialysis • G092 Continuous arteriovenous hemodiafiltration • G093 Hemodiafiltration - Contin. Init & Acute (repeatx3) • G094 Hemodiafiltration - Contin. Chronic • G095 Slow Continuous Ultra Filtration - Initial & Acute (repeat)

		• G096 Slow Continuous Ultra Filtration – Chronic • G294 Arteriovenous slow continuous ultrafiltration init and acute • G295 Continuous arteriovenous hemofiltration initial and acute • G333 Home/self-care dialysis • H540 Renal dialysis (outpatient).
3. Liver disease in the 3 years prior to cohort entry	CIHI-DAD and OHIP	CIHI-DAD: B18.x, K70.x, K71.1, K71.3–K71.5, K71.7, K72.x–K74.x, K76.0, K76.2–K76.9, Z94.4 liver disease. OHIP Diagnosis Code: 571 liver disease.
4. Alcoholism in the 3 years prior to cohort entry	CIHI and OHIP	CIHI: F102, G312, G621, G721, I426, K292, K860, Z8640. OHIP Diagnosis Code: 303
5. Dementia in the 3 years prior to cohort entry	Ontario Dementia Database (DEMENTIA)	Not applicable
6. Diabetes in the 3 years prior to cohort entry in the 3 years prior to cohort entry	Ontario Diabetes Dataset (ODD)	Not applicable
7. Hypertension: Ontario Hypertension Database in the 3 years prior to cohort entry	Ontario Hypertension dataset (HYPER)	Not applicable
8. Congestive heart failure (CHF) in the 3 years prior to cohort entry	Congestive Heart Failure (CHF)	Not applicable
9. Active Cancer	OCR, OHIP	Diagnosis in OCR within 1 year OR any of the following OHIP fee codes within 180 days: chemotherapy: G281, G339, G345, G359, G381, G382, G388; and radiation: X310, X311, X312, X313.
10. $CHADS_2$-VASc Score for Atrial Fibrillation Stroke Risk at cohort entry date	As specified for each code related.	1. Congestive heart failure (CHF database): 1 point 2. Hypertension (HYPER database): 1 point 3. Age 65-74 years: 1 point and age 75 years or older: 2 points

		4. Diabetes Mellitus (Ontario Diabetes Database): 1 point 5. Previous thromboembolism (codes as following in the preceding 3 years): Any or more than 1 of these codes leads to 2 points. Total score can be 0 or 2. 6. Vascular disease (CAD or PVD: CIHI DAD/NACRS: I25x, I70x, I71x, I73x, I74x, K55.1. OHIP: 412, 451in the preceding 3 years): 1 point 7. Female Sex: 1 point
11. HAS-BLED Score at cohort entry date: HAS-B_ED is HAS-BLED without the variable INR (with factors as defined above in the 3-y preceding entry or according to the definition of the ICES-derived cohort)	As specified for each code related.	1. Hypertension (HYPER database): 1 point 2. Abnormal renal function (codes for CKD and ESRD) described above): 1 point 3. Abnormal liver function (codes described above): 1 point 4. Stroke or TIA (CIHI-DAD: I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64, I65, I65.0, I65.1, I65.2, I65.3, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.4, I66.8, I66.9 cerebral infarction (ischemic stroke); G45.0, G45.1, G45.2, G45.3, G45.8, G45.9 transient ischemic attack (TIA)): 1 point 5. Bleeding history (bleeding codes described as following in outcome section): 1 point 6. Elderly: Age over 65: 1 point 7. Alcoholism (codes described above): 1 point
12. Charlson Comorbidity Index (using a 3-year lookback).	DAD	Derived using an ICES-developed macro
Potential drug interactions – dispensed in the past 3 months prior to cohort entry		
1. Warfarin: yes/no	ODB	Not applicable
1. Former PPIs co-therapy: yes/no	ODB	Not applicable

	Potential drug interactions – dispensed during the following up period	
1. Non-steroidal anti-inflammatory drugs*: day-to-day basis	ODB	ibuprofen, naproxen, etodolac, nabumetone, indomethacin, rofecoxib, celecoxib, etoricoxib valdecoxib, and meloxicam
2. Selective serotonin reuptake inhibitors (SSRI): yes/no.	ODB	citalopram, escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, mirtazapine, trazodone, amitriptyline, nortriptyline, imipramine, and bupropion
3. Amiodarone	ODB	Not applicable
4. Statins: yes/no.	ODB	Atorvastatin, Fluvastatin, Pravastatin, or Simvastatin
5. Aspirin*: day-to-day basis	ODB	Not applicable
6. Antiplatelets: day-to-day basis	ODB	clopidogrel, ticagrelor, dipyridamole, ticlopidine, or prasugrel
7. Antimicrobials: yes/no.	ODB	Fluconazole, Cephalexin, Cefuroxime, Cotrimoxazole, trimethoprim, Macrolides, Azithromycin, Clarithromycin, Macrolides, Ocular Antibiotics, Amoxicillin, Ampicillin, Penicillins, Gatifloxacin, Ciprofloxacin, Norfloxacin, Quinolones, or Levofloxacin
Outcomes		
Bleeding events	CIHI-DAD and CIHI-NACRS	ICD10 1. Intracranial haemorrhage: I60, I61, I62.0, I62.1, I62.9, S06.400, S06.401, S06.410, S06.411, S06.420, S06.421, S06.430, S06.431, S06.440, S06.441, S06.490, S06.491, S06.500, S06.501, S06.510, S06.511, S06.520, S06.521, S06.530, S06.531, S06.540, S06.541, S06.590, S06.591, S06.600, S06.601, S06.610, S06.611, S06.620, S06.621, S06.630, S06.631, S06.640, S06.641, S06.690, S06.691 2. Eye haemorrhage H35.6, H43.1, H45.0, H11.3, H31.3

		3. Bleeding of respiratory system: R04.0, R04.1, R04.2, R04.8, R04.9, J94.2 4. Upper GI bleeding: I85.0, I98.20, I98.3, K22.10, K22.12, K22.14, K22.16, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.80 5. Lower GI bleeding and general GI bleeding: K62.5, K55.20, K55.21, K63.80, K92.0, K92.1, K92.2 6. Urogenital system bleeding: R31, R310, R311, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N93.0, N93.8, N93.9, N95.0 7. Bleeding of muscular and skeletal systems: M25, M25.00, M25.01, M25.02, M25.03, M25.04, M25.05, M25.06, M25.07, M25.08, M25.09 8. Others: K66.1, N42.1, R58, T79.2, K66.1, D68.3
Thromboembolic event	CIHI-DAD and CIHI-NACRS	ICD10 1. Cerebral infarction (ischemic stroke): I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64, I65, I65.0, I65.1, I65.2, I65.3, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.4, I66.8, I66.9 2. Transient ischemic attack (TIA): G45.0, G45.1, G45.2, G45.3, G45.8, G45.9 3. Retinal vascular occlusions: H34.0, H34.1, H34.2, H34.8, H34.9

		4. Myocardial infarction (MI): I21.1, I21.2, I21.3, I21.4, I21.9, I22.0, I22.1, I22.8, I22.9, I23.0, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8, I24.0, I24.1, I24.8, I24.9 5. Pulmonary embolism (PE): I26.0, I26.9 6. Vascular disorders of intestine: K55.0, K55.1, K55.9 7. Systemic embolism: I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9 8. Atherosclerosis: I70.0, I70.1, I70.2, I7020, I7021, I70.8, I70.9 9. Nontraumatic ischemic infarction of muscle: M62.2 10. Thrombophlebitis: I80.0, I80.1, I80.2, I80.3, I80.8, I80.9, G08 11. Other venous embolism and thrombosis: I82.0, I82.1, I82.2, I82.3, I82.8, I82.9, I81, I67.6 12. Other peripheral vascular diseases: I73.1, I73.8, I73.9
All cause death	RPDB	Not applicable

Abbreviation: the abbreviation for databases refer to Table 1., CCI for Canadian Classification of Interventions codes.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page / lines
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 / 1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	As it is a protocol, n/a
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4 / 32-74
Objectives	3	State specific objectives, including any prespecified hypotheses	4 / 74-79
Methods			
Study design	4	Present key elements of study design early in the paper	4 / 81-83
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4 / 84-95
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4 / 96-105
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5 /108-127 & 6/153-170
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Table 2
Bias	9	Describe any efforts to address potential sources of bias	6 / 171-178
Study size	10	Explain how the study size was arrived at	5-6 / 138-152
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7 / 179-186
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7 / 187-208
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			**As it is a protocol, n/a**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	

		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	n/a
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	n/a
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	n/a
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	n/a
Generalisability	21	Discuss the generalisability (external validity) of the study results	n/a
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8 / 234-238

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.